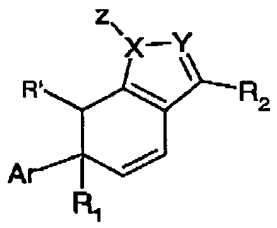
Application Ser. No.: 10/761,982
Filing Date: January 21, 2004
Examiner: Stockton, Laura

Amendment Pursuant to 37 C.F.R. § 1.121

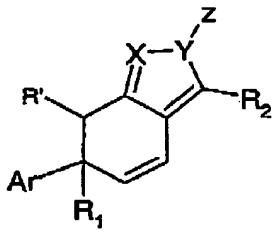
IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1. (currently amended) A compound of formula (1) or formula (2)



(1)



(2)

wherein:

X and Y ~~independently~~ are N ~~or CH wherein at least one of X and Y is N~~;

Ar is:

phenyl optionally substituted with one or more substituents selected from the group consisting of: halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, thio$(C_1\text{-}C_4)$alkyl, NO_2, NH$(C_1\text{-}C_4)$alkyl and N$((C_1\text{-}C_4)\text{alkyl})_2$ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of the phenyl wherein said 4 to 6 membered ring may contain a second hetero atom selected from the group consisting of O, S and N, ~~or~~

~~5 or 6 membered aromatic heterocycle containing one or two hetero atoms selected from the group consisting of O, N and S, and optionally substituted with one or more halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, thio$(C_1\text{-}C_4)$alkyl, NH$(C_1\text{-}C_4)$alkyl, N$((C_1\text{-}C_4)\text{alkyl})_2$ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho~~

~~carbon of said heterocycle wherein said 4 to 6 membered ring may optionally contain a second hetero atom selected from the group consisting of O, S and N,~~

Z is H, 4-aminophenyl, SO_2R_3 or COR_3 wherein R_3 is (C_1-C_4)alkyl, (C_3-C_5)cycloalkyl, Ar as defined above, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

R_1 is H, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl or Ar as defined above;

R' is H or (C_1-C_4)alkyl; and

when Z is H, R_2 is ~~a~~ selected from the group consisting of:

cyano,

C(O)-ORa_1 wherein Ra_1 is methyl, ethyl or isopropyl,

C(O)-NHRa_2 wherein Ra_2 is cyclopropyl,

C(O)-N(Ra_2'), wherein N(Ra_2') is aziridinyl or azetidinyl, optionally substituted with (C_1-C_4)alkyl or Ar as defined above,

C(O)-N(Ra_3)-ORa_3 wherein each Ra_3 may be identical or different and each Ra_3 is independently selected from the group consisting of methyl, ethyl or cyclopropyl,

C(O)Ra_4 wherein Ra_4 is Ar as defined above or (C_3-C_5)cycloalkyl optionally substituted with (C_1-C_4)alkyl or Ar as defined above,

C(Ra_4)=N-Rb wherein:

Ra_4 is H, Ar as defined above, or (C_3-C_5)cycloalkyl optionally substituted with (C_1-C_4)alkyl or Ar as defined above, and

Rb is (C_1-C_2)alkyl, (C_3-C_5)cycloalkyl, hydroxyl, (C_1-C_4)alkoxy, (C_2-C_4)alkenyloxy, or (C_1-C_4)alkylenoxy wherein said (C_1-C_4)alkylenoxy optionally may be substituted with halogen or a group selected from the group consisting of carboxyl, $(CH_2)_n$Ar wherein n is 0 or 1 and Ar is as defined above, (C_1-C_4)alkoxy, NH_2, NH(C_1-C_4)alkyl, and N$((C_1-C_4)$alkyl$)_2$ wherein said alkyls together with the heteroatom to which they are attached may optionally form a 3 to 6 membered ring which

may optionally contain a second hetero atom selected from the group consisting of O, S and N,

$NH\text{-}C(O)Ra_4$ wherein Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

$NHRa_4$ wherein Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

phenyl, and

5 to 6 membered aromatic heterocycle containing 1 to 3 hetero atoms selected from the group consisting of O, N and S; and

when Z is SO_2R_3 or COR_3, R_2 is carboxyl, NH_2, $NH(C_1\text{-}C_4)$alkyl, $N((C_1\text{-}C_4)alkyl)_2$ or $(C_3\text{-}C_5)$cycloalkylamino; or

a stereoisomeric form of the compound of formula (1) or formula (2), or mixtures of the stereoisomeric forms thereof in any ratio; or

a ~~pharmacetically~~ pharmaceutically acceptable salt of the compound of formula (1) or formula (2).

2. (original) The compound according to claim 1 wherein Ar is phenyl, 4-fluorophenyl or 4-methoxyphenyl.

3. (original) The compound according to claim 2 wherein R_1 is H, $(C_1\text{-}C_4)$alkyl, phenyl or substituted phenyl.

4. (canceled).

5. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is $C(O)\text{-}ORa_1$ and wherein Ra_1 is ~~$(C_1\text{-}C_4)$alkyl~~ methyl, ethyl or isopropyl.

6. (original) The compound according to claim 5 selected from the group consisting of:

ethyl 6,6-diphenyl-6,7-dihydro-2H-indazole-3-carboxylate,
isopropyl 6,6-diphenyl-6,7-dihydro-2H-indazole-3-carboxylate,
methyl 6,6-diphenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6-(R,S)-6-methyl-6-phenyl-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl 6-(+)-6-methyl-6-phenyl-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl 6-(R,S)-6-phenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6-(R)-6-phenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6-(S)-6-phenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6,6-bis(4-methoxyphenyl)-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl 6-(R,S)-6-(3,4-dimethoxyphenyl)-6-phenyl-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl 6-(R,S)-6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl (-)-6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl (+)-6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazole-3-carboxylate,
ethyl 6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazole-3-carboxylate, and
ethyl 7-methyl-6,6-diphenyl-6,7-dihydro-1H-indazole-3-carboxylate.

7. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is $CORa_4$ and Ra_4 is Ar or $(C_3\text{-}C_5)$cycloalkyl.

8. (original) The compound according to claim 7 selected from the group consisting of:

cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone,

cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone,
(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)phenylmethanone,
(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)-(1H-pyrrol-3-yl)methanone,
6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone,
(-)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone,
(+)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone, and
cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone.

9. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is C(O)-NHRa$_2$, C(O)-N(Ra$_3$)-ORa$_3$ or C(O)-N(Ra$_2$').

10. (original) The compound according to claim 9 selected from the group consisting of:
N-(cyclopropyl)-6,6-diphenyl-6,7-dihydro-1H-indazole-3-carboxamide,
azetidin-1-yl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone,
(N-methoxy-N-methyl)-6,6-diphenyl-6,7-dihydro-1H-indazole-3-carboxamide, and
aziridin-1-yl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone.

11. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is C(Ra$_4$)=N-Rb.

12. (original) The compound according to claim 11 selected from the group consisting of:

(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl) methanone oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl) methanone oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl) methanone oxime,
(E,Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone oxime,
(E)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone oxime,
(Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-2H-indazol-3-yl)methanone O-methyloxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-2H-indazol-3-yl)methanone O-methyloxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-2H-indazol-3-yl)methanone O-methyloxime,
(E,Z)6,6-diphenyl-6,6-dihydro-1H-indazole-3-carbaldehyde O-methyloxime,
(E, Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(E)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,

(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-methoxyethyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-methoxyethyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-methoxyethyl)oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-benzyloxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-benzyloxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-benzyloxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(4-nitrobenzyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(4-nitrobenzyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(4-nitrobenzyl)oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-dimethylaminoethyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-dimethylaminoethyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-dimethylaminoethyl)oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-fluoroethyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-fluoroethyl)oxime,

(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-fluoroethyl)oxime,
(E,Z)-6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(E)-6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(Z)-6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(-)-6-(Z)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(-)-6-(E)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(+)-6-(Z)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(E,Z)cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(Z)cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone oxime, and
(E)cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone oxime.

13. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is NH-C(O)Ra_4.

14. (currently amended) The compound according to claim 13 selected from the group consisting of:

N-(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)cyclopropylamide, and
N-[6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl]benzamide.

15. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is ~~Ar~~ phenyl, pyridyl, oxadiazolyl or thiophenyl.

16. (original) The compound according to claim 15 selected from the group consisting of:

3-(3-methyl[1,2,4]oxadiazol-5-yl)-6,6-diphenyl-6,7-dihydro-1H-indazole,

3,6,6-triphenyl-6,7-dihydro-1H-indazole,

6,6-diphenyl-3-pyrid-3-yl-6,7-dihydro-1H-indazole, and

6,6-diphenyl-3-thiophen-3-yl-6,7-dihydro-1H-indazole.

17. (currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is CN.

18. (currently amended) The compound according to ~~claim 14~~ claim 17 wherein the compound is 6,6-diphenyl-6,7-dihydro-1H-indazole-3-carbonitrile.

19. (original) The compound according to claim 1 wherein Z is SO_2R_3 or COR_3.

20. (original) The compound according to claim 19 selected from the group consisting of:

6,6-diphenyl-1-(4-toluenesulphonyl)-6,7-dihydro-1H-indazol-3-ylamine and

1-(3-Amino-6,6-diphenyl-6,7-dihydroindazol-1-yl)propenone.

21. (original) The compound according to claim 1 wherein Z is 4-aminophenyl.

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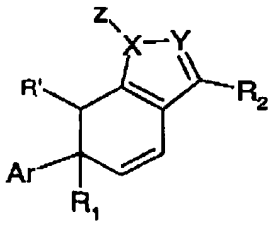
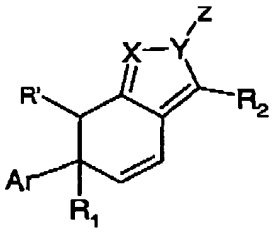
22. (original) The compound according to claim 21 wherein the compound is ethyl 1-(4-aminophenyl)-6,6-diphenyl-1H-indazole-3-carboxylate.

23. – 26. canceled

27. (currently amended) A method for the treatment of tumors comprising administering to a patient in need of said treatment a therapeutically effective amount of a compound of formula (1) or formula (2)



(1)



(2)

wherein:

X and Y ~~independently~~ are N ~~or CH wherein at least one of X and Y is N~~;

Ar is:

phenyl optionally substituted with one or more substituents selected from the group consisting of: halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, thio$(C_1$-$C_4)$alkyl, NO_2, NH$(C_1$-$C_4)$alkyl and N$((C_1$-$C_4)$alkyl$)_2$ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of the phenyl wherein said 4 to 6 membered ring may contain a second hetero atom selected from the group consisting of O, S and N, ~~or~~

~~5 or 6 membered aromatic heterocycle containing one or two hetero atoms selected from the group consisting of O, N and S, and optionally substituted with one or more halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, thio$(C_1$-$C_4)$alkyl, NH$(C_1$-$C_4)$alkyl, N$((C_1$-$C_4)$alkyl$)_2$ wherein said alkyl may optionally form a 4 to 6 membered ring~~

~~together with the heteroatom to which it is attached and an ortho carbon of said heterocycle wherein said 4 to 6 membered ring may optionally contain a second hetero atom selected from the group consisting of O, S and N,~~

Z is H, 4-aminophenyl, SO_2R_3 or COR_3 wherein R_3 is $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, Ar as defined above, $(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

R_1 is H, $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl or Ar as defined above;

R' is H or $(C_1$-$C_4)$alkyl; and

when Z is H, R_2 is a selected from the group consisting of:

cyano,

C(O)-ORa_1 wherein Ra_1 is methyl, ethyl or isopropyl,

C(O)-$NHRa_2$ wherein Ra_2 is cyclopropyl,

C(O)-$N(Ra_2')$, wherein $N(Ra_2')$ is aziridinyl or azetidinyl, optionally substituted with $(C_1$-$C_4)$alkyl or Ar as defined above,

C(O)-$N(Ra_3)$-ORa_3 wherein each Ra_3 may be identical or different and each Ra_3 is independently selected from the group consisting of methyl, ethyl or cyclopropyl,

C(O)Ra_4 wherein Ra_4 is Ar as defined above or $(C_3$-$C_5)$cycloalkyl optionally substituted with $(C_1$-$C_4)$alkyl or Ar as defined above,

C(Ra_4)=N-Rb wherein:

Ra_4 is H, Ar as defined above, or $(C_3$-$C_5)$cycloalkyl optionally substituted with $(C_1$-$C_4)$alkyl or Ar as defined above, and

Rb is $(C_1$-$C_2)$alkyl, $(C_3$-$C_5)$cycloalkyl, hydroxyl, $(C_1$-$C_4)$alkoxy, $(C_2$-$C_4)$alkenyloxy, or $(C_1$-$C_4)$alkylenoxy wherein said $(C_1$-$C_4)$alkylenoxy optionally may be substituted with halogen or a group selected from the group consisting of carboxyl, $(CH_2)_n$Ar wherein n is 0 or 1 and Ar is as defined above, $(C_1$-$C_4)$alkoxy, NH_2, $NH(C_1$-$C_4)$alkyl, and $N((C_1$-$C_4)$alkyl$)_2$ wherein said alkyls together with the heteroatom to which they are attached may optionally form a 3 to 6 membered ring which

may optionally contain a second hetero atom selected from the group consisting of O, S and N,

$NH\text{-}C(O)Ra_4$ wherein Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

$NHRa_4$ wherein Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

phenyl, and

5 to 6 membered aromatic heterocycle containing 1 to 3 hetero atoms selected from the group consisting of O, N and S; and

when Z is SO_2R_3 or COR_3, R_2 is carboxyl, NH_2, $NH(C_1\text{-}C_4)$alkyl, $N((C_1\text{-}C_4)alkyl)_2$ or $(C_3\text{-}C_5)$cycloalkylamino; or

a stereoisomeric form of the compound of formula (1) or formula (2), or mixtures of the stereoisomeric forms thereof in any ratio; or

a ~~pharmacetically~~ pharmaceutically acceptable salt of the compound of formula (1) or formula (2).

28. (original) The method of claim 27 wherein the therapeutically effective amount comprises an amount sufficient to inhibit microtubule polymerization.

29. (original) The method of claim 27 wherein the therapeutically effective amount comprises a therapeutically effective endothelial cell detaching amount.

30. (original) The method of claim 27 wherein the therapeutically effective amount comprises an amount sufficient to inhibit vascularization of said tumors.

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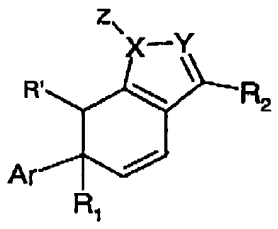
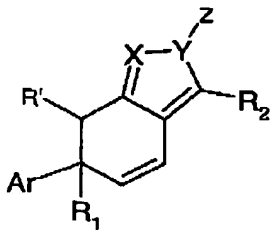
31. (currently amended) A method for the treatment of cancerous cells comprising administering to a patient in need of said treatment a therapeutically effective amount of a compound of formula (1) or formula (2)



(1)



(2)

wherein:

X and Y ~~independently~~ are N ~~or CH wherein at least one of X and Y is N~~;

Ar is:

phenyl optionally substituted with one or more substituents selected from the group consisting of: halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, thio$(C_1$-$C_4)$alkyl, NO_2, NH$(C_1$-$C_4)$alkyl and N$((C_1$-$C_4)$alkyl$)_2$ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of the phenyl wherein said 4 to 6 membered ring may contain a second hetero atom selected from the group consisting of O, S and N, ~~or~~

~~5 or 6 membered aromatic heterocycle containing one or two hetero atoms selected from the group consisting of O, N and S, and optionally substituted with one or more halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, thio$(C_1$-$C_4)$alkyl, NH$(C_1$-$C_4)$alkyl, N$((C_1$-$C_4)$alkyl$)_2$ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of said heterocycle wherein said 4 to 6 membered ring may optionally contain a second hetero atom selected from the group consisting of O, S and N,~~

Z is H, 4-aminophenyl, SO_2R_3 or COR_3 wherein R_3 is $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, Ar as defined above, $(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

R_1 is H, $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl or Ar as defined above;

R' is H or $(C_1\text{-}C_4)$alkyl; and

when Z is H, R_2 is a selected from the group consisting of:

cyano,

C(O)-ORa_1 wherein Ra_1 is methyl, ethyl or isopropyl,

C(O)-NHRa_2 wherein Ra_2 is cyclopropyl,

C(O)-N(Ra_2'), wherein N(Ra_2') is aziridinyl or azetidinyl, optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

C(O)-N(Ra_3)-ORa_3 wherein each Ra_3 may be identical or different and each Ra_3 is independently selected from the group consisting of methyl, ethyl or cyclopropyl,

C(O)Ra_4 wherein Ra_4 is Ar as defined above or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

C(Ra_4)=N-Rb wherein:

Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above, and

Rb is $(C_1\text{-}C_2)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, hydroxyl, $(C_1\text{-}C_4)$alkoxy, $(C_2\text{-}C_4)$alkenyloxy, or $(C_1\text{-}C_4)$alkylenoxy wherein said $(C_1\text{-}C_4)$alkylenoxy optionally may be substituted with halogen or a group selected from the group consisting of carboxyl, $(CH_2)_n$Ar wherein n is 0 or 1 and Ar is as defined above, $(C_1\text{-}C_4)$alkoxy, NH_2, NH$(C_1\text{-}C_4)$alkyl, and N$((C_1\text{-}C_4)\text{alkyl})_2$ wherein said alkyls together with the heteroatom to which they are attached may optionally form a 3 to 6 membered ring which may optionally contain a second hetero atom selected from the group consisting of O, S and N,

NH-C(O)Ra_4 wherein Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

NHRa_4 wherein Ra_4 is H, Ar as defined above, or $(C_3\text{-}C_5)$cycloalkyl optionally substituted with $(C_1\text{-}C_4)$alkyl or Ar as defined above,

phenyl, and

5 to 6 membered aromatic heterocycle containing 1 to 3 hetero atoms selected from the group consisting of O, N and S; and

when Z is SO_2R_3 or COR_3, R_2 is carboxyl, NH_2, $NH(C_1\text{-}C_4)$alkyl, $N((C_1\text{-}C_4)alkyl)_2$ or $(C_3\text{-}C_5)$cycloalkylamino; or

a stereoisomeric form of the compound of formula (1) or formula (2), or mixtures of the stereoisomeric forms thereof in any ratio; or

a ~~pharmacetically~~ pharmaceutically acceptable salt of the compound of formula (1) or formula (2).

32. (original) The method of claim 31 wherein the therapeutically effective amount comprises an amount sufficient to inhibit microtubule polymerization.

33. (original) The method of claim 31 wherein the therapeutically effective amount comprises a therapeutically effective endothelial cell detaching amount.

34. (original) The method of claim 31 wherein the therapeutically effective amount comprises an amount sufficient to inhibit vascularization of said cancerous cells.

35. (original) A pharmaceutical composition comprising one or more compounds of formula (1) or formula (2) according to claim 1 and one or more pharmaceutically acceptable carriers, diluents, adjuvants or excipients.